PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61L 25/00 — A1

(11) International Publication Number: WO 96/13285

(43) International Publication Date: 9 May 1996 (09.05.96)

(21) International Application Number: PCT/GB95/02543

(22) International Filing Date: 30 October 1995 (30.10.95)

(30) Priority Data:

9421967.2	28 October 1994 (28.10.94)	GB
9516933.0	18 August 1995 (18.08.95)	GB

(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(71) Applicant *(for all designated States except US)*: INNOVATIVE TECHNOLOGIES LIMITED [GB/GB]; Road Three, Winsford Industrial Estate, Winsford, Cheshire CW7 3PD (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: QIN, Yimin [GB/GB]; 123 Victoria Road, Northwich, Cheshire CW9 5RQ (GB). GILDING, Keith, Dennis [GB/GB]; Nepenthe, Winsford Road, Wettenhall, Winsford, Cheshire CW7 4DL (GB).

(74) Agent: ATKINSON, Peter, Birch; Marks & Clerk, Sussex House, 83-85 Mosley Street, Manchester M2 3LG (GB).

(54) Title: DEHYDRATED HYDROGELS

(57) Abstract

A dehydrated hydrogel incorporating a plasticiser and fibres which have provided cations for cross-linking the dehydrated hydrogel.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

DEHYDRATED HYDROGELS

The present invention relates to dehydrated hydrogels which are useful in the treatment of wounds.

A hydrogel is a cross-linked macromelecular network swollen with water or biological fluids. A dehydrated hydrogel is a cross-linked macro-molecular network that will swell to form a hydrogel upon contact with water or biological fluids. Due to their 'dehydrated' condition, dehydrated hydrogels are easy to store and transport. In addition, when applied in the dry state to a wound they behave as superabsorbent materials.

According to a first aspect of the present invention there is provided a dehydrated hydrogel incorporating a plasticiser and fibres which have provided cations for cross-linking the dehydrated hydrogel.

According to a second aspect of the present invention there is provided a method of producing a dehydrated hydrogel comprising dispersing fibres into an aqueous solution of a hydrogel precursor material incorporating a plasticiser. the fibres incorporating cations which are capable of cross-linking said precursor material to form a hydrogel, and evaporating water to produce a dehydrated hydrogel which incorporates said fibres, the dehydrated hydrogel being cross-linked by said cations.

The dehydrated hydrogel may be in the form of a film having a thickness of, for example, 20 microns to 1 mm.

The dehydrated hydrogels of the invention have a number of advantages. In particular, the presence of the fibres imparts strength and dimensional stability to the dehydrated hydrogel. Furthermore films of the dehydrated hydrogels have the property of swelling in only the thickness dimensions and not in the other two dimensions (as compared to films of conventional dehydrated hydrogels which swell in all three dimensions).

Typically, dehydrated hydrogels in accordance with the invention will comprise (based on the total weight of the fibres, polymer forming the hydrogel, and plasticiser, i.e. excluding water and other components) 15 to 40% by weight of fibres, 10 to 35%, and 5 to 75% plasticiser. More preferably the fibres and polymer together provide about 40-60% ideally about 50% by weight on the same weight basis so that correspondingly the plasticiser provides 60-40%, ideally about 50%. generally the amount of fibres will exceed the amount of polymer. For example the weight ratio may be 1.5-3:1. Typically the dehydrated hydrogel will contain less than 50% by weight of water, ideally less than 20%, based on the total weight of the dehydrated hydrogel.

Examples of hydrogel precursor material which may be used include sodium alginate, sodium carboxymethyl cellulose, sodium pectinate, sodium O-carboxymethyl chitosan (OCC), sodium N,O-carboxymethyl chitosan (NOCC), sodium polyacrylate, and naturally occurring gums and synthetic polymers containing pendant carboxylic acid groups (hummectants).

The hydrogel precursor may consist wholly or partially of Ace Mannan (or other component of Alloe Vera) which is a natural polymer known to accelerate healing of

wounds. The Ace Mannan may, for example, provide up to 80% of the matrix. The Ace Mannan may be clinical grade material obtainable from Carrington Laboratories, Dallas, Texas, U.S.A.

The fibres which are used contain a di- or higher valent cation which is effective for cross-linking the hydrogel. Examples of suitable cations include Ca^{2+}, Zn^{2+}, and cations which also act as enzyme cofactors. Particular preferred examples of fibres which may be used are calcium alginate fibres. The fibres will generally have a length of 1 to 80 mm and a thickness of 10 to 50 microns.

The fibres may be such that they absorb water from the aqueous solution of the hydrogel precursor material during manufacture of the dehydrated hydrogel.

Examples of suitable plasticisers include glycerol, polyethylene glycol, sorbitol and similar sugars, and pluronic type PEO/PPO polymers.

In a typical method of preparing a dehydrated hydrogel in accordance with the invention, the fibres, polymer and plasticiser in their relative requisite amounts are admixed with water such that the fibres, polymer and plasticiser together provide less than 5% by weight (e.g. less than 3%, e.g. 2%) of the resultant mixture. After thorough mixing, the dispersion may be cast to an appropriate thickness and water evaporated to give a dehydrated hydrogel product containing less than 50% water, more usually 20% or less.

Dehydrated hydrogels in accordance with the invention have a number of advantages. In particular when applied to the wounds (e.g. donor sites, abrasions, dermabrasions, surface wounds with high exudate or wide savings in exudate levels)

they are capable of absorbing large amounts of exudate, e.g. up to 30 times their own weight, thereby rehydrating to form a hydrogel. If the dehydrated hydrogel is in the form of a film, it is found that the film swells in the thickness dimension without substantial swelling in the other two dimensions. Upon sufficient absorption of exudate, the film is capable of dissolving. The product of the invention is more absorbent than current commercial hydrogels, and is also light and easy to package.

Dehydrated hydrogels in accordance with the invention may be laminated to hydrophilic films which have an increased breathability in the presence of liquid water as compared to moisture vapour alone. The use of such a film over the dehydrated hydrogel (i.e. on the side remote from the wound) ensures that water is vented from the dehydrated hydrogel through the film. Therefore the dissolution of the hydrogel may be controlled.

Typically the breathable film will be of a material which, as a 50 micron film, has an MVTR in the presence of moisture vapour alone of 6,000 to 10,000 g m^{-2} $24hr^{-1}$ as measured by ASTM E96B and an MVTR in the presence of liquid water (as measured by ASTM E96BW) of 6,000 to 10,000 g m^{-2} $24hr^{-1}$. Typically the breathable film will have a thickness of 30-70 microns, more preferably 40-60 microns, e.g about 50 microns.

The breathable film may for example be of polyurethane. Suitable films are available from Innovative Technologies Limited under the designations IT325, IT425 and IT625.

If desired, the dehydrated hydrogel may incorporate an active agent (e.g. an antimicrobial material) for delivery to a wound.

The invention will be further described by the following non-limiting Examples.

Example 1

7 kg of calcium alginate fibres having a length of 3-6 mm were dispersed in 500 litres of water. Separately, a solution of 3 kg sodium alginate in 60 litres of water was prepared and 10 kg glycerol added thereto. The sodium alginate/glycerol solution and the fibre dispersion were thoroughly mixed and the resultant admixture made up to 1,000 litres.

The mixture was cast at 4 kg/m^2 to give a thickness of 4 mm. Drying was then effected in an air current under IR at 30°C so that the film contained less than 50% of water.

The resultant product was a dehydrated hydrogel which was capable of absorbing at least 10 times its own weight of water.

Example 2

1 g calcium alginate fibre (chopped into 20 mm lengths) was dispersed into an aqueous medium containing 0.5 g NOCC and 1.5 g glycerol. The resultant mixture was then cast into a 16 x 23 cm stainless steel dish and the solvent evaporated overnight in an oven at 80°C.

The resultant film had the properties of both NOCC and alginate fibres.

Example 3

1 g of calcium alginate fibre (chopped into 20 mm length) was dispersed into 100 ml distilled water. Separately, 0.5 g of sodium alginate powder (Protanal LF10/60 from Pronova Biopolymers) were mixed with 100 ml of distilled water. A third 100 ml portion of distilled water was mixed with 0.15 g Acemannan powder (from Carrington Laboratories).

The three liquid were then mixed together with 1.65 g of glycerol. After thorough mixing, the mixture was cast into a 16 x 23 cm stainless steel disc and the solvent evaporated overnight in an oven at 80°C.

The resultant film comprised a dehydrated hydrogel having the wound healing properties of the Acemannan.

CLAIMS

1. A dehydrated hydrogel incorporating a plasticiser and fibres which have provided cations for cross-linking the dehydrated hydrogel.

2. A dehydrated hydrogel as claimed in claim 1 in the form of a film.

3. A dehydrated hydrogel as claimed in claim 2 wherein the film has a thickness of 20 microns to 1 mm.

4. A dehydrated hydrogel as claimed in any one of claims 1 to 3 comprising 15 to 40% by weight of fibres, 10 to 35% by weight of polymer and 5 to 75% by weight of plasticiser, the percentages being based on the total weight of fibres, polymer and plasticiser.

5. A dehydrated hydrogel as claimed in claim 4 wherein the fibres and polymer together provide about 40-60% by weight on the same weight basis as defined in claim 4.

6. A dehydrated hydrogel as claimed in any one of claims 1 to 5 wherein the amount of fibres exceeds the amount of polymer.

7. A dehydrated hydrogel as claimed in claim 6 wherein the weight ratio of fibres:polymer is 1.5-3:1.

8. A dehydrated hydrogel as claimed in any one of claims 1 to 7 containing less than 50% by weight of water.

9. A dehydrated hydrogel as claimed in claim 8 containing less than 20% by weight of water.

10. A dehydrated hydrogel as claimed in any one of claims 1 to 9 wherein the fibres have a length of 1 to 80 mm.

11. A dehydrated hydrogel as claimed in any one of claims 1 to 10 wherein the fibres have a thickness of 10 to 50 microns.

12. A dehydrated hydrogel as claimed in any one of claims 1 to 11 wherein the plasticiser is glycerol, polyethylene glycol, sorbitol or a PEO/PPO polymer.

13. A dehydrated hydrogel as claimed in any one of claims 1 to 12 which comprises Acemannan as said dehydrated hydrogel.

14. A dehydrated hydrogel which comprises Acemannan as the dehydrated hydrogel, and which further comprises a plasticiser and fibres capable of providing cations.

15. A dehydrated hydrogel as claimed in claim 14, wherein the Acemannan provides up to 80% of the dehydrated hydrogel.

16. A method of producing a dehydrated hydrogel comprising dispersing fibres into an aqueous solution of a hydrogel precursor material incorporating a plasticiser, the fibres incorporating cations which are capable of cross-linking said precursor material to form a hydrogel, and evaporating water to produce a dehydrated hydrogel which incorporates said fibres, the dehydrated hydrogel being cross-linked by said cations.

17. A method as claimed in claim 16 wherein the hydrogel precursor material is selected from sodium alginate, sodium carboxymethyl cellulose, sodium pectinate, sodium O-carboxymethyl chitosan (OCC), sodium N,O-carboxymethyl chitosan (NOCC), sodium polyacrylate, and naturally occurring gums and synthetic polymers containing pendant carboxylic acid groups (hummectants).

18. A method as claimed in claim 16 or 17 wherein the fibres contain Ca^{2+}, Zn^{2+} and/or cations which also act as enzyme cofactors.

19. A method as claimed in any one of claims 16 to 18 wherein the fibres are calcium alginate fibres.

INTERNATIONAL SEARCH REPORT

International Application No
PC., GB 95/02543

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 613 693 (JOHNSON & JOHNSON MEDICAL) 7 September 1994 see claims; examples ---	1-19
Y	EP,A,0 459 378 (FIDIA SPA) 4 December 1991 see examples 1-7 ---	1-19
P,Y	WO,A,95 00184 (CARRINGTON LAB INC) 5 January 1995 see page 27, line 15 - line 32; claims ---	1,2,14, 15
A	EP,A,0 567 311 (SQUIBB BRISTOL MYERS CO) 27 October 1993 see claims; examples 1-3 ---	1-19
A	WO,A,90 14110 (VILAIN JEAN) 29 November 1990 see claims ---	1-19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 1996	12.03.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	ESPINOSA, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 16245 (SMITH & NEPHEW) 1 October 1992 see claims	1
A	EP,A,0 216 378 (STATNI VYZKUMNY USTAV TEXTILNI) 1 April 1987 see claims	1

3

INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
PC.,GB 95/02543

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0613693	07-09-94	GB-A-	2275686	07-09-94
		AU-B-	5755694	08-09-94
		CA-A-	2116743	04-09-94
		JP-A-	6343684	20-12-94
EP-A-0459378	04-12-91	IT-B-	1248666	26-01-95
		AU-B-	7806791	05-12-91
		CA-A-	2043450	01-12-91
		IN-A-	172300	05-06-93
		JP-A-	4235124	24-08-92
WO-A-9500184	05-01-95	US-A-	5409703	25-04-95
		AU-B-	7115394	17-01-95
EP-A-0567311	27-10-93	AU-B-	3703593	28-10-93
		CA-A-	2094533	23-10-93
		JP-A-	6009373	18-01-94
		NZ-A-	247431	27-11-95
WO-A-9014110	29-11-90	AU-B-	5561690	18-12-90
		EP-A-	0472575	04-03-92
		JP-T-	4505267	17-09-92
WO-A-9216245	01-10-92	AT-T-	130766	15-12-95
		AU-B-	657122	02-03-95
		AU-B-	1435992	21-10-92
		DE-D-	69206407	11-01-96
		EP-A-	0576523	05-01-94
		GB-A,B	2268885	26-01-94
		JP-T-	6507793	08-09-94
EP-A-216378	01-04-87	NONE		